

like a toxemia. I did make a diagnosis of epilepsy and a cataleptic state, and gave her thyroid, believing that she needed this to combat whatever protein poisoning was in her system. The coma and cataleptic attacks entirely disappeared. She had one or two epileptic attacks, however, and later a few petit mal attacks. The menstruation became regular and on time, and the patient entirely recovered. She married in 1905, and was well until 1910, when I saw her last. There were no other symptoms in her case of subthyroid secretion, except that she did not menstruate on time, and that she had these periodic toxic attacks. I now feel sure she had Raynaud's syndrome, with the cerebral vessels affected, associated with a subthyroid secretion.

CONCLUSIONS. 1. Raynaud's disease is not a distinct entity; it is a syndrome caused by the disturbance of one or more internal secreting glands.

2. There is primarily no real disease of the bloodvessels, but the vasomotor control is so abnormally disturbed that most profound contraction of certain bloodvessels may occur in different parts of the body, perhaps more or less coincident with abnormal dilatation of other bloodvessels. If the contracted bloodvessels are peripheral the parts more or less lose their function and show various trophic disturbances.

3. This bloodvessel spasm may occur in the internal organs of the body as well as peripherally, though much less frequently and more difficult of diagnosis.

4. The syndrome is probably due to disturbances of more than one of the ductless glands of the body that have internal secretion, but there is always apparently some disturbance of the thyroid gland, perhaps a diminution of the vasodilator stuff of this gland.

5. Judiciously applied, thyroid treatment improves the majority of cases, perhaps all, and cures some cases. Nitroglycerin is always of temporary benefit and local heat is always of immediate benefit.

OBSERVATIONS ON A CASE OF FAMILY PERIODIC PARALYSIS.

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WE have to report some observations upon a case of family periodic paralysis. The case was studied very carefully, from a

neurological point of view, by Taylor¹ in 1898. The present investigations lie entirely in the field of chemical pathology.

The literature on the subject was very completely reviewed up to 1898 in Taylor's paper.

In 1901 Singer² gave a critical digest of the literature up to that date, with bibliography. Fairly complete bibliographies will also be found in the papers of Kramer, 1908,³ and Gatti, 1911.⁴

Kramer counted 78 cases in the entire literature, and since that time probably not more than a dozen have been reported.

The neurological aspect of the disease has been carefully studied by a large number of observers, notably Goldflam,⁵ Oppenheim,⁶ Taylor,⁷ Mitchell,⁸ and Oddo and Darcourt.⁹ A discussion of the etiology of the disease will be found in Singer's¹⁰ and in Buzzard's¹¹ papers.

Pieces of muscle have been excised by Goldflam, Oppenheim, Crafts,¹² and Singer. All have described the microscopic appearances as "abnormal." Oppenheim found waxy degeneration. Goldflam and Crafts described the fibers as being hypertrophied and vacuolated, and Crafts also says that there is an increase in fibrous tissue. Singer found extensive fissuring in the cut sections which he considered an artifact, but which he thinks would not have been present unless there were "some essential abnormality in the muscle fibers to produce such uniform and unusual appearances."

The toxicity of the urine during an attack and interval have been studied of Goldflam, using Bouchard's method, who found that "during attacks there was a distinct increase in the urotoxic coefficient, the increase in some cases being nearly fourfold." This author found that the knee-jerk was diminished in rabbits after the injection of urine collected during an attack, but failed to get changes in the electrical reactions. Singer, using the same method, found that during an attack the urine was definitely more toxic than during an interval. Mitchell, also using this method, found no difference in the urotoxic coefficient before and during an attack. These findings are of purely historical interest.

¹ Family Periodic Paralysis, *Jour. Nerv. and Ment. Dis.*, 1898, xxv, 637. Continued same, p. 719.

² Case of Family Periodic Paralysis with Digest of Literature, *Brain*, 1901, xxiv, 257.

³ Zur Frage der Periodischen Paralyse der Extremitäten, *Russische Medizinische Rundschau*, 1908, vi, 454.

⁴ La Paralyse Périodique, *Gaz. d. hôp.*, Paris, 1911, p. 1327.

⁵ See Taylor, loc. cit.

⁶ See Taylor, loc. cit.

⁷ Loc. cit.

⁸ Case of Family Periodic Paralysis, *AMER. JOUR. MED. SCI.*, 1899, cxviii, 513.

⁹ Les réactions électriques dans la paralysie familiale périodique, *Archiv d'Electric. Med.*, 1902, xi, 1.

¹⁰ Loc. cit.

¹¹ Three Cases of Family Periodic Paralysis, *Lancet*, London, 1901, ii, 1564.

¹² Fifth Case of Family Periodic Paralysis, *AMER. JOUR. MED. SCI.*, 1900, cxix, 651.

The toxicity of the blood serum was studied by Mitchell and by Mitchell, Flexner, and Edsall,¹³ but the results were apparently negative.

Crafts has extracted from the feces during an attack a toxic substance which, when injected into rabbits and guinea-pigs, produced a transient paralysis. He does not appear to have controlled his results. Two authors, Mitchell and Mailhouse,¹⁴ on attempting to draw blood for examination found that it clotted with great rapidity, but did not determine the coagulation time by any accurate method.

Upon the urine a large amount of work has been done. Mitchell has made analyses of total nitrogen, urea, uric acid, sulphur, and phosphates, but does not give the diet in detail, so that the significance of the results is uncertain. Crafts found an increase in ethereal sulphates during an attack, but he also fails to record the diet. The same is true of Singer's complete analyses.

Mitchell, Flexner, and Edsall¹⁵ determined the total nitrogen of the food and urine and of ammonia and creatinin in the urine, the latter by the old Neubauer-Salkowski method (before Folin's method was published), which is undoubtedly far from accurate. The ammonia was continuously low, and the creatinin was very low for a day or two before attacks, and during the first part, and rising sharply, just after or during the latter part of the attacks.

Holtzapple¹⁶ made a large number of urinary examinations, urea and indican being the chief things recorded. The diet is not mentioned, nor the method for determining urea. In general (average of a large number of cases), he found that the urea elimination seemed below normal and the indican increased.

Mailhouse has found a striking reduction in calcium and magnesium in spite of the fact that his patient was on a liberal diet containing more or less milk. He also found in the urine on several occasions a proteose-like body which decreased during attacks, and in addition practically always found creatin in the urine. The creatinin was somewhat higher just before the attack rather than afterward, as in Mitchell, Flexner, and Edsall's case. The methods used are not given, nor is the diet recorded in detail. Several authors have mentioned a high indican test during attacks; the same has been found to be true in our case.

Atwood¹⁷ found in one of his cases that the intestinal flora contained a marked preponderance of the *Bacillus aërogenes capsulatus*.

In regard to the ordinary blood examination, moderate leukocytosis has been found by Goldflam, Taylor, and by Singer.

¹³ Physiological and Chemical Study of Three Cases of Family Periodic Paralysis, *Brain*, 1902, xxv, 109.

¹⁴ Observations on a Case of Family Periodic Paralysis, *Jour. Nerv. and Ment. Dis.*, 1910, xxxvii, 209.

¹⁵ *Loc. cit.*

¹⁶ Family Periodic Paralysis, *Penn. Med. Jour.*, 1903, vii, 408.

¹⁷ Family Periodic Paralysis, *New York State Jour. Med.*, 1913, xii, 579.

The most recent papers on this disease are those of Gardner,¹⁸ who reports a typical case, and discusses the etiology and treatment, and of Diller and Rosenbloom,¹⁹ who studied the nitrogen, sulphur, calcium, magnesium, phosphate, and fat metabolism during an interval only.

Gardner believed the condition to be due to an intoxication, and on that hypothesis treated his patient by catharsis, low protein diet, avoidance of alcohol, together with caffeine, digitalis, and bromides during an attack, and got marked improvement.

The only positive findings of Diller and Rosenbloom were a marked decrease in creatinin and an increase in undetermined nitrogen. The average creatinin coefficient was 4.8.

CASE REPORT.—The clinical data on our case are as follows:

J. T. S., male, aged thirty-five years; weight 83.6 kilograms.

The disease has been in the family for five generations; the history is absolutely typical, namely, attacks of complete flaccid paralysis of all the skeletal muscles save those of the face, of deglutition, and of the eye muscles, lasting from six to forty-eight hours, and coming on at irregular intervals, the longest interval being seldom over six days, the sphincters and diaphragm not being involved, the reflexes and electrical reactions being diminished, or abolished during the height of the more severe attacks, and the patient being perfectly well in the intervals. Normal respiration was not involved in the paralysis, but the accessory muscles apparently were, for during the more severe attacks the patient was unable to take a deep inspiration or make a forcible expiration.

A complete genealogy showing the line of descent and the afflicted members in each generation is given in Taylor's paper.²⁰ Since the appearance of that paper a case has arisen in the sixth generation, a niece of the patient, aged nine years, having had several rather mild but characteristic attacks.

The patient came to the hospital at our request merely for purposes of investigation. He was in the medical wards from April 7 to May 8, 1914. During this time he had a number of attacks, some severe and some mild. The sequence and severity of the attacks are indicated in the accompanying chart. Those of April 15, April 21-22, and of May 1, were severe, there being complete paralysis of the arms, legs, trunk, and neck muscles, lasting twelve hours or more. Several other attacks, lasting a shorter period, and in which the paralysis was less complete, likewise occurred.

A complete clinical description of the attacks is also given in Taylor's paper, and since during the present stay in the hospital the attacks were entirely similar, it will be unnecessary to go into details here.

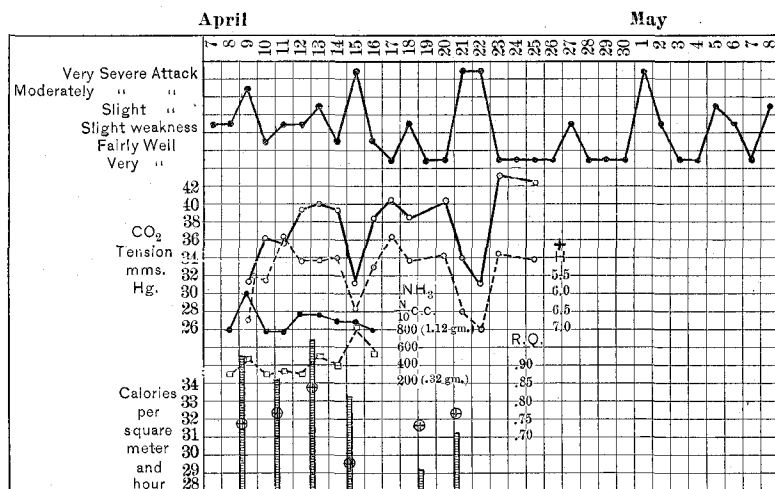
¹⁸ Case of Periodic Paralysis, *Brain*, 1913, xxxv, 243.

¹⁹ Family Periodic Paralysis, *Arch. Int. Med.*, 1914, xiv, 869.

²⁰ *Loc. cit.*

The physical examination save for an enlarged spleen (felt two fingers' breadth below the costal margin, with increase in splenic dullness) was negative. The skeletal muscles were unusually well developed, so much so in fact that the possibility of a pseudo-muscular hypertrophy was suggested. However, since the patient had a perfectly normal degree of muscular ability, being in fact rather athletic, taking much exercise, such as bicycle riding, swimming, and bowling, between attacks, this was ruled out.

Several writers have described dilatation of the heart, increase in pulse rate, and other signs of cardiac weakness during attacks. No evidence of any such occurrence was found in our case.



The upper curve indicates the patient's condition as regards paralysis from day to day. The CO₂ tension by the Plesch method is shown by solid lines and circles; by the Lindhard method, broken lines and circles. The ammonia in cubic centimeters of a N/10 solution and also in grams is shown by broken lines and squares; the hydrogen ion concentration of the urine by solid lines and dots; the respiratory quotients by circles containing crosses, and the basal metabolism in calories per square meter and hour, by perpendicular columns. The first four basal metabolism determinations are with the Benedict, the last two with the Douglas apparatus.

The urine was negative to ordinary examination save for a rather high amount of indican, which increased during attacks. This increase may not improbably be explained by the constipation which always occurred with the attacks.

There never was any albumin except after the administration of large doses of sodium bicarbonate, and the presence of albumin, under such circumstances, cannot be considered abnormal.²¹

There were never any sugar, urobilogen, or acetone bodies.

²¹ Palmer, W. W., and Henderson, L. J., *Clinical Studies on Acid Base Equilibrium*, Arch. Int. Med., 1913, xii, 153.

Blood smear was negative. Wassermann test on the blood was negative.

EXPERIMENTAL OBSERVATIONS.—The findings of Goldflam, Oppenheim, and Taylor that the electrical reactions of the muscles are diminished or abolished during attacks suggest at once that the abnormality lies in the muscle itself or the end plate rather than in the nervous system. Such an abnormality might be produced by an alteration in the intermediate metabolism of the muscle cell or by some disorder of general metabolism leading to the elaboration of some circulating toxin having some special action upon muscle.

With a view to gaining information on the second alternative we have carried out the following investigations:

First of all we determined the basal metabolism. The determinations of April 9, 11, 13, and 15 were made with the Benedict respiration apparatus. The method has been described and the significance of basal metabolism discussed in a previous paper by one of us (J. H. M.).²² The determinations of April 19 and 21 were made with a type of respiration apparatus devised by C. G. Douglas,²³ in which the expired air is collected in a rubber bag and analyzed. The gaseous exchange was determined in each of these experiments by five periods of five minutes each, on the apparatus. The figures for CO₂ and O₂ in the five periods were averaged and the calory output determined by indirect calorimetry.²⁴ With both types of apparatus the patient was examined in the morning during complete muscular rest, and in the *nüchtern* condition. The results of these experiments are shown in the chart. The metabolism is expressed as calories per square meter of body surface per hour. The body surface was calculated from Meeh's formula.²⁵

With a view to finding out whether any acidosis occurred during the attacks, the alveolar carbon dioxide tension was determined daily from April 9 through April 23. Two methods were used: (1) Four of the so-called B samples of Lindhard were taken and the results averaged. The method has been described by Lindhard.²⁶ (2) A determination by the Plesch method²⁷ was made. The Lindhard method gives the CO₂ tension of the arterial, the Plesch of the venous blood. The Plesch determinations, therefore, are always a few millimeters higher than the Lindhard, but should show similar fluctuations if an acidosis is present.

²² Studies of Basal Metabolism in Obesity and Pituitary Disease, Jour. Med. Research, 1915, xxvii, 121.

²³ Jour. Physiol., vol. xlii; Method for Determining Respiratory Exchange, Proc. Phys. Soc., 1911, vol. xvii.

²⁴ Williams, Riche, and Lusk, Animal Calorimetry II, Jour. Biol. Chem., 1914, xii, 349.

²⁵ Body surface = $2.3\sqrt{\text{weight}^2 \text{ (grams)}}$.

²⁶ Excitability of Respiratory Centre, Jour. Physiol., 1911, xlii, 343. See also Krogh, A., Apparatus for Study of Muscular Work, Skand. Archiv. f. Physiol., 1913, xxx, 383.

²⁷ Hämodynamische Studien, Ztschr. f. Exper. Path. u. Therap., 1909, vi, 380.

An inspection of the results which are given in the chart will show a striking fall in both sets of samples occurring with the attacks of April 9, 15, and 21 to 22.

These drops in CO_2 tension at once suggested that an acidosis was present during attacks, so certain other tests were carried out to throw further light on the subject, but unfortunately failed to do so.

The hydrogen ion concentration of the urine was determined by the method of Henderson and Palmer.²⁸ In the attack of April 9 it increased from 6.5 to 5.5, but showed no rise in that of April 15.²⁹

The titratable acid in the urine was not increased during the attacks.

The urinary ammonia showed a rise in the attacks of April 15, but not in that of April 9.

The response to alkali both during intervals and attacks was normal, namely, after the ingestion of 5 grams of sodium bicarbonate, marked decrease in the hydrogen ion concentration occurred within two hours, and was accompanied by a decrease in the ammonia, apparently corresponding to that found in normal individuals.³⁰

Determinations of the lactic acid in the blood and in the urine, both during an attack and in an interval, were made by Ryffel's method.³¹ The results were all within normal limits. The blood varied from 10 to 21 mgm. per 100 c.c. and the urine from 11 to 16 mgm. per twenty-four hours.

An attempt to find further evidence of an acidosis was also made by determining the dissociation curve of CO_2 free blood by Barcroft's method.³² This constitutes a test for an excess of non-volatile acids in the blood. The results were negative; specimens of blood taken both during an attack and interval gave approximately the same percentage saturation when exposed to an atmosphere of 17 mm. of oxygen tension, the figure being 62 per cent. interval, 58 per cent. in an attack; the normal limits given by Barcroft being from 65 per cent. to 75 per cent.

The total nitrogen and creatinin in the urine showed nothing abnormal. On a purin-free diet the total nitrogen in the urine was from 10 to 13 grams per day. The creatinin showed no changes during attacks as compared with the intervals. It was regularly about 1.5 grams per day. Creatin was occasionally present both

²⁸ Intensity of Urinary Acidity, *Jour. Biol. Chem.*, 1913, xiii, 393.

²⁹ We are indebted to Dr. Palmer for the hydrogen ion determinations, the ammonia and titratable acidity of the urine and the lactic acid determinations on blood and urine.

³⁰ Henderson, L. J., and Palmer, W. W., Extreme Variation of the Concentration of Ionized Hydrogen in Human Urine, *Jour. Biol. Chem.*, 1913, xiv, 81.

³¹ Method for Lactic Acid in Urine, *Jour. Physiol.*, vol. xxxix; *Proc.*, p. 5.

³² Lewis, Ryffel, Wolf, Cotton, and Barcroft, *Dyspnea in Cardiac and Renal Patients*, Heart, 1913, v, 45.

during attacks and in the intervals, being from 0.1 to 0.2 grams per day.

The blood showed a high non-protein nitrogen content. Three observations, two during an attack, one during an interval, showed the same result, 74 mgm. per 100 c.c. Uric acid and urea were retained in such proportion as would be expected with the degree of nitrogen retention. Creatinin was absent from the blood during one attack and during the interval was present within normal limits.³³

The sulphonephenolphthalein excretion was normal during an interval, 61 per cent. in an hour and ten minutes.

Indican was nearly always present in the urine and showed a marked increase during attacks, but on a low protein diet there was but a trace, except during an attack, when it again increased.

The patient was seen again on January 9, 1915. After leaving the hospital in May, at our advice (because of high blood nitrogen), he went on a low protein (no meat) diet and remained on the same until the middle of September. During this period he was singularly free from attacks; never stayed in bed later than 11 A.M. all summer. In the fall he returned to a general diet and has continued it ever since. From October 15 to November 15 he had several rather mild attacks. Since then he has been better than ever in his life. Three-quarters of the time he has been up at 7 A.M. and never has been in bed later than noon. In the latter part of November he began to work on a steady job (outdoor salesman), a thing he has never done before.

A specimen of blood was examined for non-protein nitrogen, on this visit of January 9, 1915, and was found approximately the same as when in the hospital, 67 mg. per 100 c.c. of blood. The urine contained a moderate amount of indican, otherwise was negative.

DISCUSSION. Of the above observations, the fall in CO_2 tension is by far the most striking. Since the curves taken by two entirely different methods are in close agreement we feel that they are perfectly reliable. The possible known explanations for a fall in the CO_2 tension are the development of an acidosis and an increased sensitivity of the respiratory centre.

The latter might be produced by the stimulating action upon the centre of some circulating toxin. The methods used in searching for other evidence of an acidosis proved negative, except that in one attack there was an increase in the hydrogen ion concentration of the urine and in another, a rise in the ammonia. No evidence was found for supposing it to be a lactic acidosis. The Barcroft test showed no evidence of an increase in the non-volatile acids in the blood. The reaction to alkali being normal both during

³³ We are indebted to Dr. W. Denis for the nitrogen and creatinin determinations in the urine and blood.

attacks and intervals is strong evidence against an acidosis in the ordinary sense. As mentioned above, there never were any acetone bodies in the urine.

We therefore are strongly inclined to the hypothesis that the fall in CO_2 tension is due to an increased sensitivity of the centre, and the most likely cause for this would seem to be an intoxication of some sort.

In regard to the basal metabolism it will be noticed that the results with the Douglas apparatus are both lower than any with the Benedict apparatus. This is undoubtedly the result of a systematic error with the Douglas apparatus, due to a decreased ventilation of the lungs, since the subject breathes against a slightly increased pressure. However, the two Douglas experiments should be comparable one with another, though not with those done by the Benedict method.

The experiments (both methods) were all quite satisfactory with the exception of that of April 15, in which the different periods were not in close agreement and the R. Q. gave an impossible value, being below 0.7. The R. Q.'s in all the other experiments were between 0.78 and 0.88, which is as close as is often obtained on different days in the same individual. Disregarding then the experiment of April 15, we find that the basal metabolism determined with the Benedict apparatus on April 9 and 13 (days on which there was an attack) was higher than on April 11, when he was fairly well. Also, that in the case of the Douglas experiments, that of April 21, a severe attack, gave a higher value than that of April 19, when he was unusually well. In other words, the basal metabolism of this patient is apparently higher during attacks than in the intervals. This is rather extraordinary, for one would expect the metabolism to be lower during the enforced, and hence more complete muscular rest present while the patient is paralyzed. This increase in metabolism might reasonably be interpreted as being a further bit of evidence in favor of an intoxication.

The retained non-protein nitrogen in the blood is interesting, but we are at a loss to explain it. The urine showed no evidence of nephritis; there was no cardiac hypertrophy or hypertension, and the phthalein excretion was normal. It is also of interest to note that the retained nitrogen persisted after eight months, although during that time there had been marked improvement in the periodic palsy.

The creatinin in the urine showed no change during attacks, as was found in the case reported by Mitchell, Flexner, and Edsall.³⁴ The creatinin coefficient was 6.6, which is nearly up to the normal low limit of 7 given by Shaffer.³⁵ Hence the low coefficient found by Diller and Rosenbloom³⁶ is not a constant feature in this disease.

³⁴ Loc. cit.

³⁵ Excretion of Creatin and Creatinin, Amer. Jour. Physiol. 1908, xxiii, 1.

³⁶ Loc. cit.

No definite conclusions can be drawn from these scattered observations. We think, however, enough positive findings were obtained to make it seem probable that this disease is one of metabolism and not of nervous origin. The question of acidosis is certainly worthy of further study,³⁷ and the hydrogen ion concentration of the blood might yield valuable information. We had not the facilities for performing this test.

Gardner's case showed a striking improvement on eliminative treatment and low protein diet. Also in our case an improvement dated from the time he began such a diet, though when he returned to a general diet the improvement continued. It is only fair to bear in mind that many observers have reported a tendency for this disease to improve with age, so it is quite possible that J. T. S.'s improvement was part of the natural sequence of events and had nothing to do with the low protein diet.

We should hardly agree with Diller and Rosenbloom, who thought that their patient's freedom from attacks while in the hospital was due to the low protein diet that he was getting. He had just had a very severe attack; in our patient's case after a very severe attack he is nearly always unusually well for a week or so. We do believe, however, that a low protein diet is worthy of a trial, and may, over a long period of time, have some influence over the number and severity of the attacks.³⁸

THE ROLE OF SYPHILIS IN HYPERTENSIVE CARDIOVASCULAR DISEASE.¹

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THE steadily increasing mortality from diseases of the cardiovascular system at a time when the deaths from the communicable diseases are decreasing, is a problem of great seriousness. The victims, for the most part, are not from the ranks of the aged who have run their course, but from those who have just attained that

³⁷ The patient has for several years been in the habit of taking potassium citrate when he felt an attack coming on. He is not certain whether it ever did any good.

³⁸ At the suggestion of Dr. W. B. Cannon, the effect of adrenalin was tried in one attack; the tendency of adrenalin to lessen the fatigability of muscle being the point in mind. Adrenalin 1 to 1000 solution Mxv, was given subcutaneously every hour for three doses. The blood-pressure was raised 12 mm., but no change at all was found in the paralysis.

The effect of physostigmin was also tried in an attack. Gr. $\frac{1}{160}$ was given every hour for four doses (subcutaneously). This also failed to have any apparent effect on the paralyzed muscles.

¹ Read before the Hartford Medical Society, April 5, 1915.